12, line 26 through page 13, line 5.) In addition, as inappropriate expression of a small *hap* transcript occurs in hepatoma and hepatoma-derived cell lines, the *hap* gene is believed to be causatively involved in liver oncogenesis. (See page 26, lines 6-28 of the specification.)

Claims 1-14, 24-34, 39-57 and 59 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over the Petkovich et al. publication in view of the Hauptmann et al. and Krust et al. publications. The Examiner asserts that the disclosure of Petkovich et al. relating to the isolation of further members of the nuclear receptor multigene family together with the contemporary knowledge of the art of molecular biology as exemplified by Hauptmann et al. and Krust et al. would have lead one skilled in the art to isolate the claimed cloned DNA sequence. Applicants respectfully traverse this rejection under Section 103.

The unobviousness and patentability of new chemical compounds are determined by taking into consideration their structure, biological and pharmacological properties. In re Papesch, 137 U.S.P.Q. 43, 51 (C.C.P.A. 1963). Applicants' DNA sequence of the RAR-β gene differs in structure, sequence and biological activity from the RAR-α gene disclosed in Petkovich et al., and is therefore patentable over the RAR-α gene.

Applicants' DNA sequence and the gene of Petkovich et al. are structurally different as they differ in their nucleotide sequences. The nucleotide sequence of the RAR-β gene of the present invention is disclosed, for example, on page 6, lines 1-22 of the present application. When compared with the sequence of

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

the RAR-α gene disclosed in Figure 2 of Petkovich et al., it is clear that the sequences are only distantly related with significant differences existing in the N-terminal regions of the encoded receptors. In view of these structural differences, it is not surprising that RAR-α and RAR-β are recognized in the art to be different retinoic acid receptors. (See Brand et al., Nature **332**:850-853 (1988), a copy of which is attached as Exhibit 5.)

Applicants' DNA sequence of the RAR-β gene further differs from the Petkovich et al. gene encoding the RAR-α retinoic acid receptor as applicants' DNA sequence has different properties from the prior art. Applicants' gene and the prior art gene map to different chromosomes. The RAR-α gene of Petkovich et al. maps to chromosome 17q21.1. (See page 448, second column.) In contrast, applicants' DNA sequence of the RAR-β gene is found on chromosome 3p24. (See Mattei et al., Hum. Genet. **80**:189-190 (1988), a copy of which is attached as Exhibit 6.) Thus, the two retinoic acid receptor genes have different biological origins.

Applicants' DNA sequence also differs in its spatial pattern of expression from the Petkovich et al. gene. As indicated in column 2 on page 449 of Petkovich et al., mRNA transcripts of the RAR-α gene were widely distributed, found in the brain, thymus, spleen, lung, liver, prostate and kidney tissues. There is no suggestion or indication, however, in the prior art that the level of mRNA transcripts found in the various tissues differed.

This is in clear contrast to the tissue expression of the DNA sequence of the present invention. Messenger RNA transcribed from the DNA sequence of the RAR-β gene of the claimed invention was

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

found to be overexpressed in the prostate and kidney. (See, for example, page 12, line 26 through page 13, line 5.) In addition, low levels of the RAR-β transcripts were also found in adult and fetal liver tissues. (See also, page 43, lines 7-19 and page 45, line 16 through page 47, line 7.) Thus, applicants' RAR-β gene and the RAR-α gene of Petkovich et al. have different biological properties as evidenced by the spacial pattern of expression.

Ligand regulation of the expression of the RAR-β receptor encoded by the DNA sequence of the claimed invention also differs from that of the RAR-α receptor of Petkovich et al. The RAR-β is transcriptionally upregulated by retinoic acid in a protein synthesis-independent fashion. Transcriptional expression of RAR-α, in contrast, is not regulated by retinoic acid. (See page 42, lines 10-15 and 22-25; and page 47, line 8 through page 49, line 16.)

The retinoic acid receptor encoded by the DNA sequence of the claimed invention also differs in its biological activity from that of the RAR-α retinoic acid receptor disclosed in Petkovich et al. in that applicants found a small transcript of the RAR-β receptor that was expressed in hepatoma and hepatoma-derived cell lines. This altered form of the retinoic acid receptor may correlate with hepatocellular transformed state. There is no suggestion in Petkovich et al, that the activity of RAR-α may correlate with any transformed state, much less with hepatocellular transformation.

These differences in structure, sequence and biological activity render the DNA sequence of the claimed invention both

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

unexpected and unobvious over the gene encoding retinoic acid receptor RAR-α of Petkovich et al.

The Examiner further contends, however, that

> [t]he Discussion section of the Petkovich et. al. reference specifically suggests that "[t]he approach used here to clone hRAR could obviously be used to isolate further members of the nuclear receptor multigene family which may be expressed in embryonic or adult tissues." This reference further states that [t]he finding that, in human hepatoma, the hepatitis B virus genome is inserted into a genomic sequence (hORF) closely related to that of the hRAR gene raises the possibility that altered retinoid receptors may have oncogenic properties." It is clear that the Petkovich et.al reference more that [sic, than] suggested the instant invention because one of ordinary skill would have found the isolation of a cDNA corresponding to hORF as described in the Related human genomic sequence section of this reference, which is the instant invention, to have been virtually anticipated by this reference. (Paper No. 21.)

Contrary to the Examiner's assertion, the speculation in Petkovich et al. does not enable the skilled artisan to reasonably predict the successful discovery and cloning of the DNA sequence of the RAR-β gene. At most the disclosure of Petkovich et al. may make it obvious to try to isolate another gene in the retinoic acid receptor family from the human genome. Obvious to try, however, is not the proper standard for an obviousness rejection. Rather a reference or combination of references must provide a suggestion and a reasonable expectation of success.

The teachings of the cited references fail to enable the skilled artisan to reasonably predict the successful discovery

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

and isolation of another gene in the human genome that is related to the hRAR gene because they fail to provide the skilled artisan with any guidance as to the direction to pursue in order to clone applicants' gene.

The general speculation in Petkovich et al. may have encouraged the skilled artisan to do further investigation, but it would not have proved to be sufficient to enable the skilled artisan to reasonably predict the successful isolation of the RAR-β gene of the claimed invention. The skilled artisan would have had no idea how many related genes might exist, there could be none or there could be hundreds.

Further, Petkovich et al. provides the skilled artisan with no guidance or direction as to which gene(s) to attempt to isolate and clone. Without such a suggestion, it would have required undue experimentation on the part of the skilled artisan to select the RAR-β gene of the claimed invention for cloning from the unknown numbers of possible members of the retinoic acid receptor family.

Moreover, the secondary references relied upon by the Examiner do not address, much less cure, these deficiencies of Petkovich et al. Hauptmann et al. relates to the identification and isolation of new sequences related to IFN-α. The reference is silent with regard to the isolation of other members of the retinoic acid receptor family.

Krust et al., which relates to the cloning of the chicken oestrogen receptor, also fails to address the deficiencies described above.

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000